



TITLE:

# Michael and Some Related Reactions

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### 3. Michael and Some Related Reactions

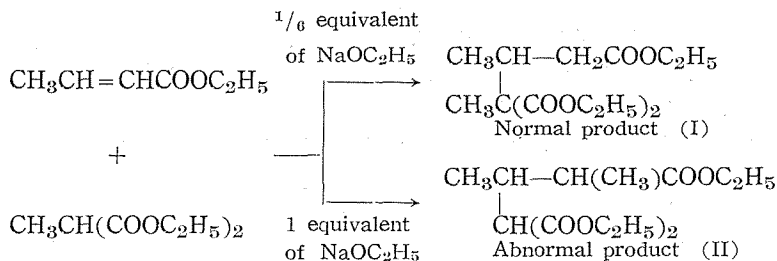
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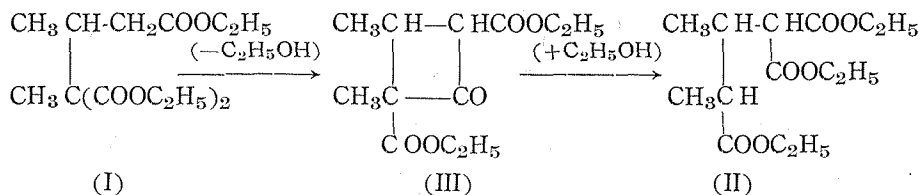
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There have been presented many papers dealing with Michael reactions. Connor<sup>1)-2)</sup> summarized a variety of the reactions and gave discussions on the relation between the structure and the reactivity of the reactants. Recently, Henneka<sup>3)</sup> interpreted the reaction mechanism in terms of the classical electronic theory.

An abnormality<sup>5)-11)</sup>, which is found in the reaction between alkylmalonic and crotonic esters, seems to be of some interest from the theoretical viewpoint.



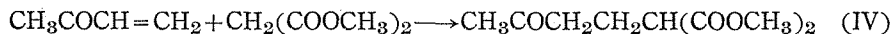
To account for the formation of this abnormal product, Michael<sup>5)-11)</sup> assumed the direct migration of methyl group from the malonate to the  $\alpha$ -carbon of crotonate. An alternative mechanism was proposed by Holden<sup>12)</sup> who assumed that the primary addition product (I) undergoes the Dieckmann condensation followed by decomposition of the cyclobutanone ring (III).



Gardner and Rydon<sup>13)</sup> criticized both the mechanisms and gave some generalizations about the reactivity. The present author<sup>14)</sup>, studying the reaction between fumaric and ethylmalonic esters, revealed that (i) the variations in either the concentration of condensing agent or the reaction period as well as the temperature had little effect on the total yield of the addition products; (ii) the content of the abnormal product in the adduct was increased linearly with the concentration of sodium ethoxide;

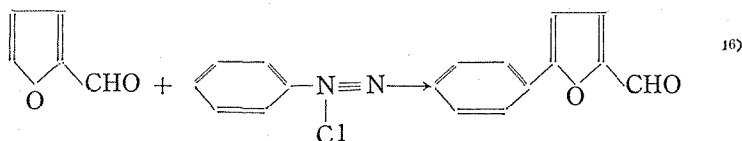
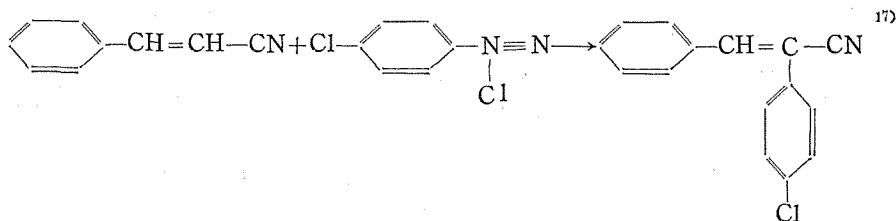
and (iii) the shorter reaction period or the lower temperature favoured the formation of the normal product. From these results, the author concluded that the reaction probably proceeds in two stages, *i.e.*, rapid formation of primary intermediate at the first step and the successive removal of sodium from it or the slower isomerization to the abnormal product at the second stage.

Despite of the Connor's generalization, it is still difficult to predict the possibility or the ease with which Michael reaction proceeds. Since a Michael reaction using methyl vinyl ketone as an unsaturated component has not yet been studied in detail<sup>15)</sup>, some experiments have been carried out. The experiments showed this unsaturated ketone can readily give an adduct with a usual active methylene compound such as malonic ester.

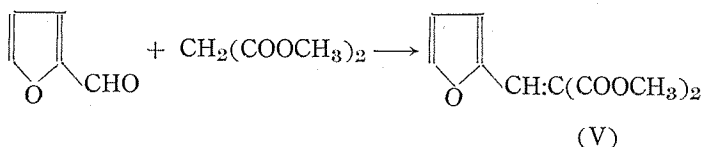


Nitromethane or *p*-thiocresol also reacts with methyl vinyl ketone to give rise to an Michael type adduct.

Furfural<sup>16)</sup> has recently been reported to undergo a Meerwein type<sup>17)</sup> condensation with diazonium salts.

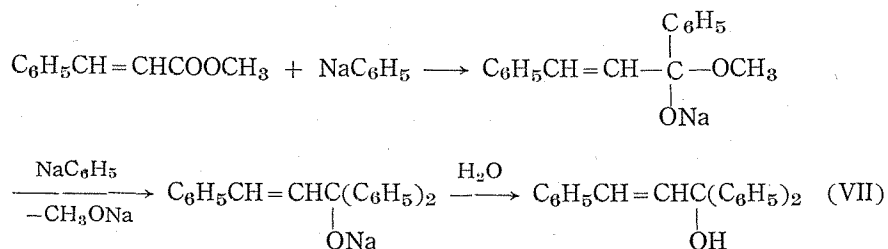


The author doubts if this reaction proceeds along an ionic mechanism. However, it may safely be assumed the furfural can react, in some cases, in the same manner as  $\alpha,\beta$ -unsaturated carbonyl compounds do. An examination on the possibility of Michael type reaction between furfural and malonic ester showed the condensation occurred only at the aldehyde group.



Addition reactions of some Grignard reagents or organoalkalimetal compounds to the  $\alpha,\beta$ -unsaturated carbonyl compounds are of interest in connection with the

Michael reaction. A reaction of phenylsodium with cinnamic ester was examined and was ascertained to proceed along the following course.



Finally, benzyl sodium was reacted with ethyl acetate where about the equal quantities of ketone and carbinol were obtained as the reaction products.

### Experimental

#### 1. Michael Reactions of Methyl Vinyl Ketone

##### i. Malonic ester as addendum.

To a solution of 0.9 g. of metallic sodium in absolute methanol was added 48 g. (0.36 mole) of dimethyl malonate, then 20 g. (0.3 mole) of methyl vinyl ketone in 50 g. methanol. The mixture was cooled with cold water so as to maintain the temperature about 10°. It took some 30 minutes to finish the addition. After being allowed to stand at the room temperature for two days, the reaction mixture was added acetic acid to neutralize the alkali present. Methanol was evaporated *in vacuo*, water was added to the residue and the separated oily layer was extracted several times with ether. The ether extract was washed with water, dried on the anhydrous sodium sulfate, the solvent was evaporated and the residue was distilled at reduced pressure. Fifteen grams of a viscous oil boiling 170°–190° at 40 mm. was obtained. This oil could be hydrolyzed by alkali, and gave a white crystalline matter (m.p. 153°–153.5°) on treating with semicarbazide.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{17}\text{O}_5\text{N}_3$  : N, 16.28.

Found : N, 16.35.

##### ii. Nitromethane as addendum.

By acting on methyl vinyl ketone with nitromethane in the same manner as with malonic ester, an addition product was obtained. However, the details of this reaction have been omitted here because there has recently been published<sup>15)</sup> a series of Michael reactions using various nitroparaffins and methyl vinyl ketone.

##### iii. *p*-Thiocresol as addendum.

To a mixture of 3 g. of sodium sand, which was prepared as usual<sup>18)19)</sup>, and 100 g. of xylene was added 16 g. (0.12 mole) of *p*-thiocresol in 50 g. of xylene, then 9 g. (0.12 mole) of methyl vinyl ketone in 20 g. of xylene under the vigorous stirring.

The reaction temperature was controlled to keep about  $10^{\circ}$ . In the course of about thirty minutes after the last drop of the thiocresol solution the stimulant odour of the keton had altogether faded away. After dissolving the sodium sand with methanol, the mixture was added water and was shaken to remove unreacted thiocresol. The xylene layer was washed with water, dried on anhydrous sodium sulfate, the solvent was evaporated and the residue was fractionated *in vacuo*. Twelve grams of colourless oil boiling  $135^{\circ}$ – $140^{\circ}$  at 13 mm. was obtained. The oil gave crystals with semicarbazide: m.p.  $158^{\circ}$ – $159^{\circ}$  (recrystallized from methanol-benzene).

*Anal.* Calcd. for  $C_{12}H_{17}ON_3S$ : N, 16.71.

Found: N, 16.34.

## 2. Condensation between Furfural and Malonic Ester

Forty grams (0.3 mole) of dimethyl malonate was added to a solution of 1.2 g. (0.05 atom) of metallic sodium in 50 g. of absolute methanol. Agitation was started, and 29 g. (0.3 mole) of furfural in 25 g. of methanol was added through a dropping funnel. The temperature was controlled to maintain about  $10^{\circ}$ . After adding all the furfural solution, the mixture was allowed to stand at room temperature for five days. Glacial acetic acid was added to interrupt the reaction, the solvent was evaporated *in vacuo*, water was added to the residue and the separated oil layer was extracted with ether. Ether extract was washed thoroughly with water, dried on the anhydrous sodium sulfate and was evaporated on a steam bath. Distilling the residue at 17 mm., 23 g. of a viscous oil, boiling at  $173^{\circ}$ , was obtained. This oil was observed to turn slowly to a crystalline matter which melted at  $66^{\circ}$  (V). By saponification with alcoholic potash (V) gave crystals (VI) melting at  $188^{\circ}$ . Since semicarbazide failed to react with (V), it was deduced that (V) had lost its carbonyl group. This means (V) was probably furfuriden malonic ester. Melting point of (VI) mixed with an authentic furfuriden malonic acid <sup>20)</sup> showed no depression.

## 3. Some Condensation Reactions with Phenyl- and Benzylsodium

### i. Cinnamic ester and phenylsodium as reactants.

Phenyl sodium was prepared according to Gilman's method<sup>19)</sup>. Eighteen grams (0.16 mole) of chlorobenzene was added dropwise to a suspension of 7.4 g. (0.32 atom) of sodium sand in 100 ml. of dry benzene which involved 1 g. of isoamyl alcohol. The mixture was warmed spontaneously by an exothermic reaction and was cooled by water to keep its temperature about  $30^{\circ}$ – $40^{\circ}$ . After two-hour stirring, most of the chlorobenzene was converted to phenyl sodium. To this mixture a benzene solution of 6.4 g. (0.4 mole) of methyl cinnamate was added in the course of 40 minutes. The reaction temperature was about  $5^{\circ}$ . Further stirring was continued for four hours. Some methanol was added to dissolve the unreacted sodium present,

the mixture was treated with ice water and was acidified with acetic acid. The water layer was extracted with ether. The benzene layer together with the ether extracts was washed with water, dried on anhydrous sodium sulfate, the solvents were evaporated *in vacuo* which left a red viscous oily residue. The residue solidified slowly to crystals (VII). Being recrystallized from a mixture of ligroin and benzene, (VII) showed m.p. 106°–108°. The melting point agreed with that of diphenyl styryl carbinol. Identification of (VII) was carried out in the following way. A mixture of 1 g. of (VII), 30 ml. of methanol and 0.3 ml. of concentrated hydrochloric acid was heated on a steam bath for 3 hours. Crystals resulting from this mixture showed the m.p., *i.e.* 98°–99°, of methyl ether of (VII). By introducing a stream of dry hydrochloric acid gas to an ether solution of (VII), a white crystalline matter melting at 207°–210° (recrystallized from benzene-methanol) was obtained. This melting point again agreed to that of the dimer of triphenyl styryl carbinol<sup>21)</sup>. Further, the melting point of (VII) mixed with an authentic diphenyl styryl carbinol<sup>24)</sup> showed no depression.

ii. Ethyl acetate and benzyl sodium as reactants.

Benzyl sodium was prepared according to Gilman's method<sup>19)</sup>. Phenyl sodium prepared from 34 g. (0.3 mole) of chlorobenzene and 13.8 g. (0.6 atom) of sodium sand in 150 ml. of dry toluene was refluxed on an oil bath for 3 hours until the black colour of the precipitates turned to brownish black through reddish brown. The mixture was cooled to –4° and was added 26.5 g. (0.3 mole) of ethyl acetate in toluene in the course of 5 minutes under the vigorous stirring. After 2 hours stirring at about 0°, the mixture was allowed to stand overnight at room temperature and was added some methanol to dissolve the unreacted sodium present, acidified with aqueous acetic acid and the aqueous layer was shaken with toluene. The toluene layer was washed with water, dried and the solvent was evaporated. The residue was fractionated at 17 mm.

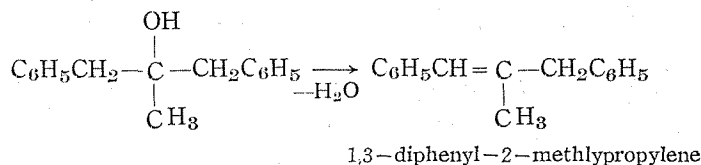
B.p.<sub>17</sub> 130°–155° an oil, 7 g. (VIII)

B.p.<sub>17</sub> 195°–200° a viscous oil, 7 g. (IX)

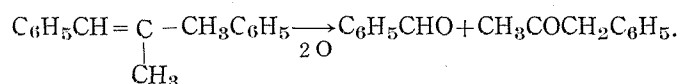
An oil (VIII) readily crystallized by ice-cooling and reacted with semicarbazide to give crystals which melted at 187°–188° (recrystallized from alcohol-benzene mixture). Mixed melting point measurement with an authentic phenyl acetone semicarbazone assured (VIII) was phenyl acetone. The viscous oil (IX) was not distinctly identified, but it is very likely that (IX) is methyl dibenzyl carbinol. Some evidences for this were as follows:

The boiling point of methyl dibenzyl carbinol was reported as 193° at 24 mm. and 182° at 15 mm.<sup>22)</sup> which nearly agreed with that of (IX). The product (IX) showed a characteristic reaction of tertiary alcohol when it was treated with Denige's reagent.

Heating 3 g. of (IX) at 160° with 5 g. of phthalic anhydride and 1 g. of phosphor pentoxide, 1.2 g. of an oily matter (X) boiling at 174°–194° (22 mm.) was obtained. This boiling point again nearly agreed with that (180° at 15 mm.) of 1,3-diphenyl-2-methyl-propylene which was prepared by Campbell <sup>23)</sup> as follows :

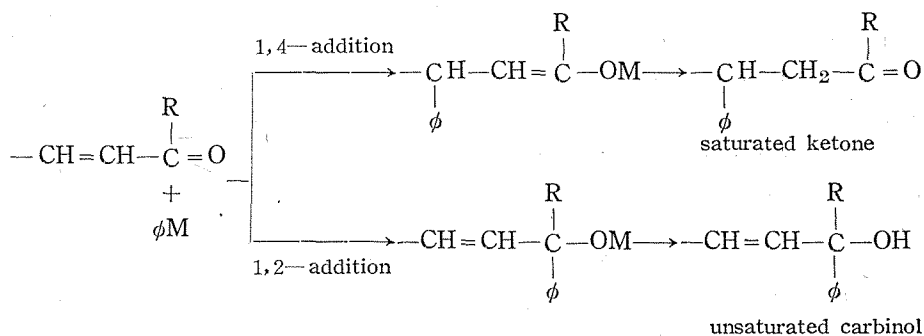


Furthermore, by oxidizing 1 g. of (X) with 2 g. of chromic acid in 15 ml. of acetic acid gave an oil (XI) which had the characteristic odour of benzaldehyde. Semicarbazide reacted with (XI) to give crystalline matter which was found to be a mixture of two substances. From their melting points, 202°–205° (VII) and 168°–172° (VIII), they were regarded as the semicarbazones of benzaldehyde and phenylacetone which were formed in the following way :

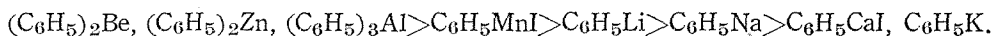


### Discussion

The addition reactions of organometallic compounds ( $\phi\text{M}$ ) to  $\alpha,\beta$ -unsaturated carbonyl compounds proceed along the following two courses.



Gilman and Kirby <sup>24)</sup> studied the reactions between benzalacetophenone or benzophenone-anil and several organometallic compounds. According to their results, the ease with which the 1,4-addition occurs falls in the following order :



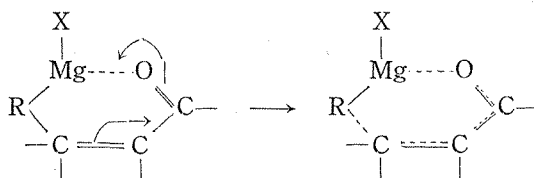
The present study, in which cinnamic ester was treated with phenyl sodium, has revealed that double 1,2-additions must have taken place, because the reaction product was diphenyl styryl carbinol (VII).

On the other hand, phenyl magnesium bromide gives a mixture of  $\beta,\beta$ -diphenyl-propionophenone  $(\text{C}_6\text{H}_5)_2\text{CHCH}_2\text{COC}_6\text{H}_5$  and methyl  $\beta,\beta$ -diphenyl-propionate  $(\text{C}_6\text{H}_5)_2\text{CHCH}_2\text{COOCH}_3$ . This means, with phenyl magnesium bromide, at least "a" 1,4-addition must have occurred. From the above examples, it can be seen that one of the most important factors in determining the course of addition is the nature of metal.

The similar situations are also found in many condensation reactions. Thus, Weizmann's condensing agents<sup>25)</sup> are prepared from higher boiling acetals and potassium hydroxide; sodium and lithium hydroxides have no effect for these condensations.

Gilman <sup>20</sup> stated the more "reactive" metallic compound does undergo 1,2-addition, but the nature of "reactive" is still obscure.

Lutz and Reveley<sup>49)</sup> assumed a six-membered ring formation in the transition state of 1,4-addition.

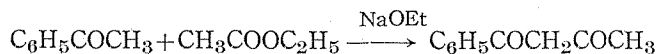


From this basis, Fuson explained the difference between the lithium and magnesium reagents in terms of the power of coordination exhibited by metals <sup>40)</sup>.

However, since Alexander and Coraor <sup>40</sup> have recently reported that the Lutz's six-membered ring mechanism is very unlikely from their experimental results, Fuson's explanation would not necessarily be correct. Theoretical and quantitative considerations from the viewpoint of nature of the metal may probably afford more accurate informations on the reaction mechanism, but such a discussion has not yet been presented.

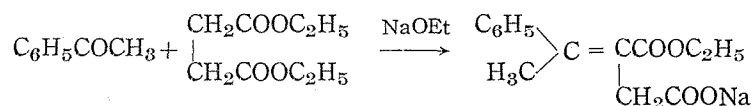
The ionic property in an organometallic compound has also marked affects upon the reaction. Sodiomalonic ester fails to condense with the ester groups, *i.e.* ethyl acetate, in contrast to phenyl- and benzyl sodium. Since sodium atom in sodiomalonic ester is evidently more positive, *i.e.* ionic, than that in phenyl or benzyl sodium, it seems to be possible to regard that the more ionic metal compounds are less reactive and the reactions will proceed in favour of 1,4-adduct formation, so far as sodium compounds are concerned.

In this connection, some related condensation reactions are of interest. Acetophenone reacts with ethyl acetate under the action of sodium alcoholate to give benzoylacetone.<sup>26)</sup>



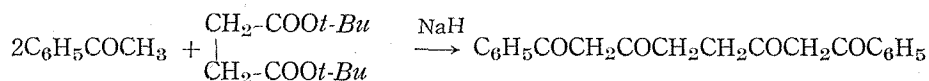


Diethyl succinate, on the other hand, undergoes an alternative type of the reaction, *i.e.* Stobbe condensation <sup>27)</sup> under the similar experimental condition :



Benzophenone also undergoes Stobbe condensation, but fails to react with ethyl or *t*-butyl acetate <sup>27)</sup>. Johnson and Daub <sup>27)</sup> accounted for this fact in terms of the ease in lactone ring formation. Recently, Sisido, Nozaki and Kurihara <sup>28)</sup> found benzophenone itself does condense with ethyl acetate by the aid of diethylamino magnesium bromide.

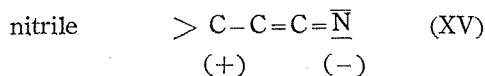
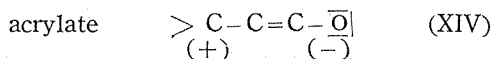
In any way, few examples <sup>29)</sup> of acetoacetic ester type condensation of succinic ester as a component has been known, but Daub and Johnson reported sodium hydride catalyzes an acetoacetic ester type condensation of acetophenone with di-*t*-butyl succinate. <sup>31)</sup>



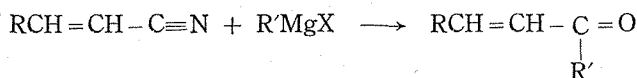
These examples indicate that the ionic property in the metal compound as well as the structure of ester group must be an important factor too.

Kohler and others <sup>31)-39)</sup> gave a series of the extensive works where various combinations of the unsaturated carbonyl and Grignard compounds were studied. The most important points of his results are that (i) only 1,2-addition takes place with unsaturated aldehyde and (ii) the formation of 1,4-adduct are more prominent with unsaturated phenyl ketones than with the methyl ketones. Colonge and his coworker <sup>37)</sup> examined the influence of the nature of alkyl group of the Grignard reagents on the course of the reaction and found the marked suppressing effect of *tert*-butyl group against the 1,2-addition. It can be seen from these studies that the more sterically favoured compounds, the more readily undergo the 1,2-addition. Highly hindered triphenyl methyl sodium, mesityl magnesium bromide and other similar compounds cannot add to the unsaturated bond but exchange their metal atom with hydrogen of  $\alpha$ -methyl group to the carbonyl, so they are able to be used as catalysts in the ester condensation <sup>29)</sup>. The difference in reactivities of benzyl- and triphenyl-sodium towards ethyl acetate is probably ascribed to the steric factor rather than the basicity.

Polarity or resonance state of the functional group of the unsaturated component also affects the reaction. In bisulfate addition reactions <sup>39)</sup>, acrylonitrile has a larger activation energy than acrylic ester does despite of the greater reaction rate of the former.



Accordingly, it can be assumed that the resonance structure (XIV) of the ester should contribute to the larger extent in the transition state of the reaction than that (XV) of the unsaturated nitrile does. Therefore 1,2-additions of organometallic compounds should take place more readily with the nitrile. Further, this tendency may be strengthened by the polar  $\text{C}\equiv\text{N}$  group. The validity of this consideration is actually supported by the following reaction <sup>30)</sup>:



where  $\text{R} : \text{C}_6\text{H}_5$  and  $\text{R}' : \text{Et}, \text{C}_6\text{H}_5\text{CH}_2$  or  $\text{C}_6\text{H}_5$ .

It is very probable to assume that Michael <sup>14)</sup>, Grignard <sup>41)</sup> and other organo-metallic <sup>42)</sup> addition reactions proceed in two stages. But there have been available few investigations <sup>43,44)</sup> about the structures of the transition intermediate. The mechanism in these reaction will be discussed more exactly from the quantitative information about the transition state.

### Summary

1. Some Michael reactions of methyl vinyl ketone were studied. Furfural was proved to undergo a Knoevenagel type condensation with malonic ester.
2. A reaction between cinnamic ester and phenyl sodium was examined where the condensation was found to proceed in favour of the 1,2-adduct formation.
3. It was shown that the differences in reactivities of various organometallic compounds toward carbonyl can hardly be accounted exactly in terms of the electronic theory.

**Acknowledgment.**—The author wishes to express his sincere thanks to Professors Ryohei Oda and Junji Furukawa for their helpful discussions and encouragement in this study.

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